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The cardiometabolic assessment of the glycemic variability in patients with diabetes mellitus: the role of the glucocardiomonitoring

Aim	To study quantitatively the two-way relationship between parameters of glycemic variability and development of cardiovascular events in patients with type 2 diabetes mellitus (DM) on chronic sulfonylurea (SM) therapy by synchronous, professional glucose and cardiac monitoring.
Material and methods	The study included 421 patients with type 2 DM on SM therapy. A 5-day synchronous glucose and cardiac monitoring was performed for these patients in a retrospective mode using an iPro2 (Medtronic, USA) continuous glycemia monitoring (CGM) system and Holter monitoring. Glycemic endpoints (CGM-parameters of glycemia variability and integral indexes) and cardiological endpoints (ventricular rhythm disorders (VRD), ST segment depression (dST), and corrected QT interval (QTc)) were evaluated.
Results	Clear correlations were found between the ST segment depression and the increase in TIR-HYPO index and the length of QTc. The strongest correlation was observed for VRD and the increase in TIR-HYPO. Moderate correlations were observed between VRD and the decrease in TIR-NORMO and between increased variabilities of glycemia (increases in SD and number of glycemia excursions >4 mmol/l/h) and integral indexes (mean CGM-level of glycemia and HbA1c). Elongation of the QTc interval was associated with increased TIR-HYPO, decrease in maximum glycemia, and development of dST.
Conclusion	The glucose and cardiac monitoring confirmed the close interrelation between the quality of glycemic control and cardiovascular disorders and should be recommended for a wider use in real-life clinical practice for determining the cardiometabolic status of patients and personalization of hypoglycemic therapy.

Keywords	Type 2 diabetes mellitus; glycemic variability; continuous glucose monitoring; glucose and cardiac monitoring; hypoglycemia; sulphonylureas; ventricular rhythm disorders; ST depression
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Introduction

From the perspective of cardiodiabetology intended to study cardiovascular complications of type 2 diabetes mellitus (DM) and dysglycemia associated with cardiovascular diseases, precise quantitative evaluation of cardiometabolic status is of immediate interest. Individual recording of the status enables timely management of metabolically interdependent regimens of hypoglycemic and multi-agent cardiovascular therapies and mitigation of metabolic complications in cardiometabolic patients. It should be pointed out that cardiovascular diseases and type 2 DM have common risk factors [1]. The mechanistic approach to cardiodiabetology provides two polar points of application. Specifically, if glycemia is the most intense primary sign, type 2 DM is diagnosed. Then, all the further events are considered as cardiovascular complications of type 2 DM. Alternatively, type 2 DM identified in patients with the pre-existing cardiological disease is considered a component of metabolic syndrome [2]. Although a patient's personalized clinical profile lies within the range, individualized cardiovascular effects of hypoglycemic agents should be taken into consideration [3]. These are sulfonylureas (SUs) in the first place, which are the most administered drugs worldwide now [4]. However, SUs are conventionally associated with increased glycemic variability [5].

Patients with type 2 DM have a long history of dysglycemia. Thus, it is necessary to quantify both integral variables and indicators of glycemic variability. Laboratory levels of glycohemoglobin (HbA1c), estimated level of glycohemoglobin (eA1c), mean levels of blood glucose, and glucose monitoring index (GMI) are the integral variables [6]. Glycemic variability as-

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sociated with type 2 DM is a quantitative indicator of the variance of glycemia from the mean value. There are more than 100 indicators of glycemic variability [7]. High glycemic variability has been specified by MAGE ≥4 mmol/L (Mean Amplitude of Glycaemic Excursion [MAGE]) for several decades [8]. Nowadays, coefficient of variation (CV) [9] and times in normo-, hypo- and hyperglycemic regions (TIR [Time in Region] system) are the most common indicators of glycemic variability [10].

High glycemic variability, hyperglycemia, and hypoglycemia may be considered as trigging factors of various cardiovascular episodes. Synchronous glucose and cardiac monitoring identifies the best association between glycemic variability and cardiovascular events [11]. Extensive evaluation of cardiometabolic status in type 2 DM with synchronous glucose and cardiac monitoring and detection of statistically significant cardiodiabetological associations are of substantial interest.

The objective of the study was to investigate a quantitative relationship between indicators of glycemic variability and cardiovascular events in patients with type 2 DM receiving SUs during qualified synchronous glucose and cardiac monitoring depending on the severity of glycemic variability, the development of hypo- and hyperglycemia.

Material and Methods

The study included 421 patients with type 2 DM admitted to the Endocrinology Department of Central Civil Aviation Clinical Hospital. Patients underwent qualified synchronous glucose and cardiac monitoring after signing the informed consent. The patients' characteristics are provided in Table 1.

A 5-day continuous glucose monitoring (CGM) was performed in an iPro2 system (MMT-7745, Medtronic, USA) to evaluate glycemic variability and integral variables. The retrospective mode was selected to prevent a patient from learning glucose levels during the procedure. Synchronous CGM and Holter monitoring (HM) using a DR200/E event recorder (NorthEast Monitoring, USA) were carried out.

Inclusion criteria: patients at the age of 30-85 years old, with type 2 DM receiving SUs; type 2 DM diagnosed more than one year ago. The functional independence in elderly patients enabling glucose and cardiac monitoring with the lowest error number. Exclusion criteria: SUs-free hypoglycemic therapy, endocrine diseases (toxic diffuse goiter, hyperparathyroidism, Cushing disease/syndrome, hyperprolactinemia), cardiac diseases (non-fatal myocardial infarction, acute coronary syndrome within 12 months before CGM, functional class (FC) 3-4 angina of effort, chronic heart failure, paroxysmal and persistent atrial fibrillation), infections, cancers, ongoing chemotherapy, pregnancy, lactation, functional dependence.

Table 1. Clinical metabolic characteristics of patients

Parameter	Value*
Age, years	64.3±8.7
Duration of diabetes mellitus, years	9.7±5.7
Weight, kg	89.6±16.9
Body mass index, kg/m^2	32.2±5.5
Glycosylated hemoglobin HbA1c, %	8.5±1.6
Atherogenicity index, U	3.4±1.4
C-reactive protein, mg/L	2.5±1.2
History of ventricular arrhythmias, %	4.5±2.5
History of FC I–II angina, %	14.2±5.6
Systolic blood pressure, mm Hg	131.7±12.1
Diastolic blood pressure, mm Hg	79.2±8.0
Heart rate, bpm	73.6±10.4

* here and later, data are expressed as "mean±standard deviation".

The study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Russian Medical Academy of Continuous Professional Education. All the patients signed informed consent.

Patients were selected for glucose and cardiac monitoring using a Statistica-generated checklist. Primary endpoints were evaluated after the end of CGM. Glycemic endpoints included: 1) indicators of glycemic variability: time in the hyperglycemic region (TIR-HYPER), time in the normoglycemic region (TIR-NORMO), and time in the hypoglycemic region (TIR-HYPO), minimum glucose level (MinGl), maximum glucose level (MaxGl), glycemic excursions >4.0 mmol/L (GE >4), standard deviation (SD), coefficient of variation (CV) and 2) integral variables: mean glycemic level measure by CGM (AvGl) and laboratory levels HbA1c before CGM (HbA1c). Primary cardiological endpoints: ventricular arrhythmias (VAs), ST-segment depression (horizontal or downsloping ST-segment depression by ≥1 mm within ≥1 min), corrected QT interval (QTc) >440 ms. VAs included frequent ventricular extrasystoles and episodes of nonsustained ventricular tachycardia.

The findings were analyzed using parametric methods of statistical analysis (normal Student's distribution) and bilateral statistics. The Pearson coefficient σ was calculated to estimate the strength of correlations. The

Table 2. Cardiodiabetological correlations (the Pearson correlation coefficient) in patients with type 2 diabetes mellitus taking sulfonylureas

Indicators	Episodes of VAs, rate of registration	QTc interval, ms	ST depression, rate of registration
QTc interval, ms	0.180	-	0.303
ST depression	0.107	0.303	-
TIR-HYPER, %	1.000	0.047	-0.028
TIR-NORMO, %	-0.446	-0.138	-0.067
TIR-HYPO, %	0.089	0.346	0.358
SD, mmol/L	0.394	0.229	0.088
Glycemic excursions >4 mmol/L/h	0.694	0.150	0.095
Mean glycemia, mmol/L	0.287	0.008	-0.100
Maximum glucose level, mmol/L	0.042	-0.313	-0.239
Minimum glucose level, mmol/L	0.454	0.132	0.004
CV, %	0.238	0.235	0.132
HbA1c, %	0.309	0.127	-0.031

TIR-HYPER, TIR-NORMO, TIR-HYPO, percentage of time in the hyper-, normo-, and hypoglycemia region; SD, standard deviation; CV, coefficient of variation; HbA1c, glycosylated hemoglobin.

data set was processed using Statistica19.0 for Windows. The level of statistical significance, $p<0.05$, was used.

Results

The findings of the 5-day glucose and cardiac monitoring in 421 patients with type 2 DM were analyzed. There were no patients excluded due to the short period of registering carbohydrate metabolism and cardiac parameters. There were no deviations from the protocol during the study. Ongoing hypoglycemic, hypotensive, hypolipidemic, and antiplatelet treatments were not adjusted during CGM.

Relationships between carbohydrate metabolism parameters registered by CGM and cardiac parameters (development of VAs, ST depression, and QTc duration) were identified in patients with type 2 DM and more than a one-year history of the who take SUs. The data are given in Table 2.

During the assessment of ST-segment depression, the highest Pearson correlation coefficient was associated with increased TIR-HYPO and prolonged QTc. The closest relationship was detected between VAs and increased TIR-HYPO. A moderate force (0.3–0.7) of correlation was noted between VAs and decreased TIR-NORMO, increased glycemic variability (higher SD and number of glycemic excursions >4 mmol/L/h) and integral variables (mean CGM-associated glucose level and HbA1c). Prolonged QTc was associated with increased CGM TIR-HYPO, decreased maximum glucose level detected by CGM, and the depression of ST-segment.

The effect of cardiac dysfunction on the quality of glycemic control and the effect of the quality of glycemic control on cardiovascular parameters were analyzed in patients with type 2 DM and a long history of the who take SUs. Glycemic parameters were stratified based on VAs, ST depression, and QTc >440 ms. The results are shown in Figure 1. The stratification of cardiac parameters based on glycemic variability, hypo-, and hyperglycemic indicators are shown in Figure 2.

Discussion

The study confirms the relationship between carbohydrate disorders and myocardial dysfunctions in patients with type 2 DM. For example, the Pearson coefficient (Table 2) allowed identifying correlations between glycemic control and cardiac dysfunction. It should be noted that the result analysis is as the most reliable concerning the multi-point parameter array produced by the multiple-day glucose and cardiac monitoring. CGM has been a standard diabetological method over the past decade [12].

However, it is usually applied without glucose and cardiac monitoring and, thus, demonstrates only detailed description of glycemic variability and precise calculation of the integral glycemic variable. Indeed, the advanced CGM interpretation is a robust tool of type 2 DM management [13]. Nevertheless, in combination with synchronous HM-ECG, it allows evaluating the origin of glycemic variability, determining cardiological factors causing higher glycemic variability, and assessing an effect of decreased glycemic variability

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Figure 1. Parameters of glycemic control based on the length of QTc interval, development of ventricular arrhythmias and ST-segment depression in patients with type 2 diabetes mellitus taking sulfonylureas

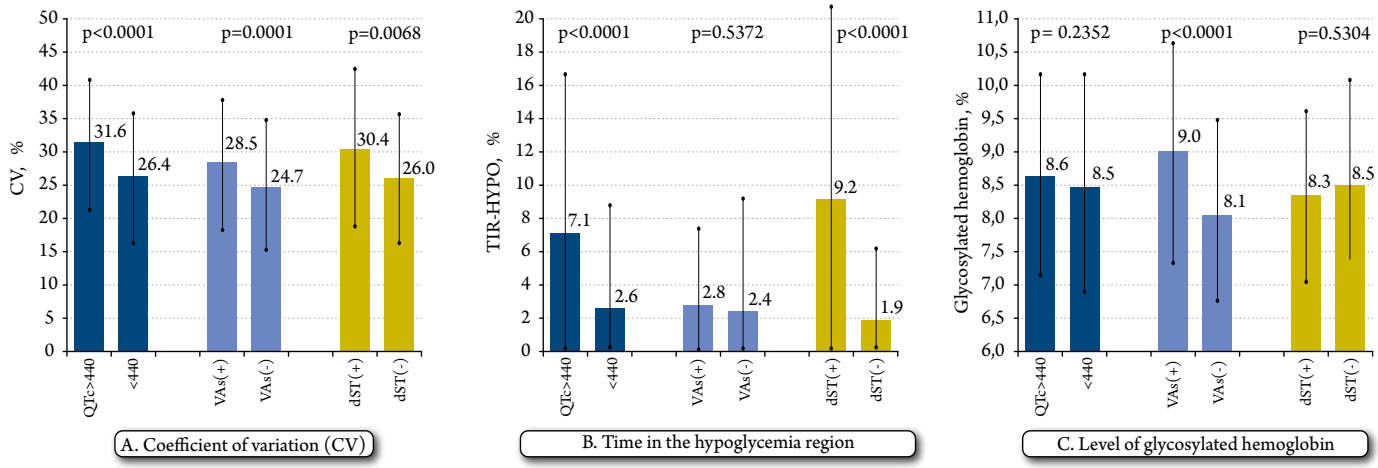
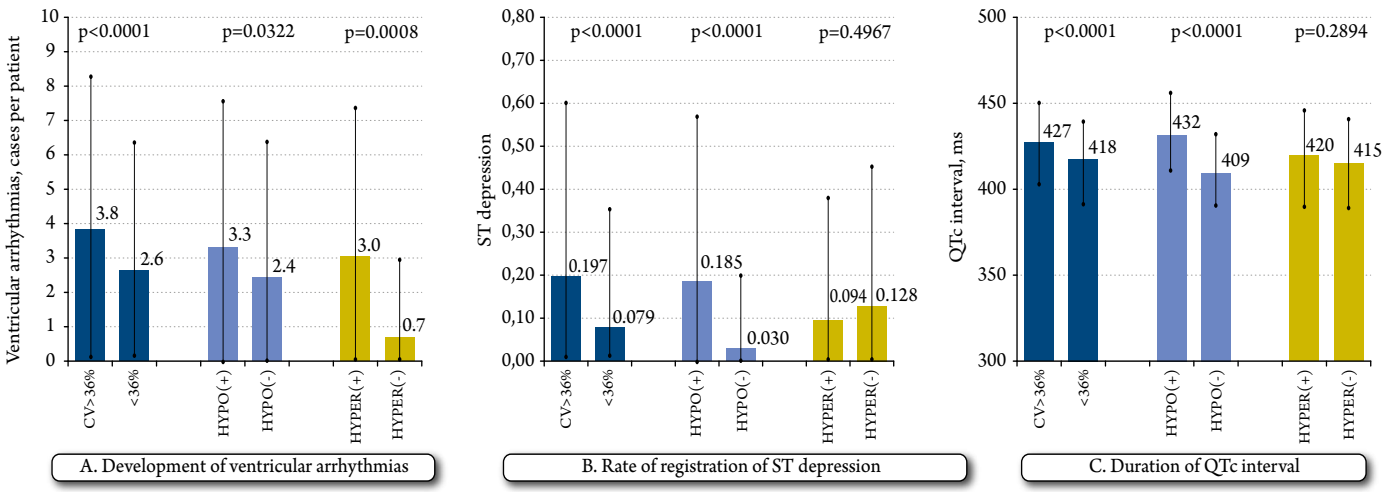


Figure 2. Parameters of cardiac dysfunction depending on the quality of glycemic control in patients with type 2 diabetes taking sulfonylureas



on mitigation of type 2 DM-associated cardiovascular complications [11].

It should be noted that a subject's clinical profile (i.e., >1-year history of type 2 DM; low-cost oral SUs therapy) is the most common. Researchers are focused on this population sample worldwide. Thus, a study carried out in the Seoul National University Hospital confirmed the onset of SUs-mediated hypoglycemias within six months, even in patients with target integral glycemic variables. At the same time, patients with type 2 DM, who reported hypoglycemia, had a significantly higher incidence of comorbid macrovascular diseases (coronary artery disease, congestive chronic heart failure, acute myocardial infarction, atrial fibrillation, peripheral arterial diseases, cerebrovascular accidents) (48.5% vs. 37.7%, p = 0.0036) [14].

Clinical use of glucose and cardiac monitoring proved that worse glycemic control, along with increased glycemic variability, cause higher variability of cardiac rhythm [15].

Myocardial ischemia and/or arrhythmia are the most common disorders of type 2 DM-compromised myocardium. For example, significantly increased glycemic variability was observed with prolonged QTc ≥440 ms, registered ST depression, and VAs, regardless of time in hyper- and hypoglycemic regions (Figure 1 A). However, a recent study compared VA patterns and glycemic profile in patients with CHF and type 2 DM and found an association between the onset of VAs and increased glycemic variability indicator MAGE. The latter was 2.2 times higher in patients with high-grade VAs than in those without VAs [16].

Prolonged QTc ≥440 ms and ST depression were associated with time in the hypoglycemic region, which was 2.7 and 4.8 times higher than non-hypoglycemic patients, respectively (p<0.0001) (Figure 1B). A sta-

tistically significant association between HbA1c and VAs was found, with higher HbA1c values in case of the development of the latter (intergroup variation +0.9%, p<0.001) (Figure 1C). Thus, our findings demonstrate a predominant association of prolonged QTc and ST depression with high glycemic variability and hypoglycemia, even in patients with target integral glycemic variables. VAs are observed both in hypoglycemia and prolonged QTc, and high hyperglycemia, which is consistent with the study of Garipova et al. [17], which included 34 patients with type 2 DM and FC II-III angina.

High glycemic variability (CV >36%), time in the hypoglycemic region (TIR-HYPO), and time in the high hyperglycemic region (TIR-HYPER) were shown to be proarrhythmic VAs-inducing factors (Figure 2A). Prolonged QTc and ST depression are associated with high glycemic variability and hypoglycemic region. However, hypoglycemia is the most potent proarrhythmic factor (Figure 2B, C).

As for patients with type 2 DM, hypoglycemic episodes associated with high glycemic variability increase the risk of arrhythmia, intensify myocardial ischemia, and macrovascular complications (acute myocardial infarction, cerebrovascular accidents) [18]. Due to persisting hypoglycemic aftereffects (reduced nitrogen oxide bioavailability, oxidative stress, platelet activation, synthesis of proatherogenic and proinflammatory cytokines), hypoglycemia has a more significant effect on the progression of atherosclerosis than low hyperglycemia or glycemic variability [19].

Thus, type 2 DM and cardiovascular diseases have common development factors. Cardiometabolic risk is associated with visceral obesity resulting in an increased risk of cardiovascular diseases and carbohydrate disorders. That is why the cardiometabolic risk was considered a component of metabolic syndrome for a long time [20].

Evaluation of glycemic variability indicators quantifying the development of hypoglycemic episodes is particularly relevant in selecting hypoglycemic treatment because therapy with SUs also contributes to cardiac arrhythmogenesis and development of myocardial ischemia caused by SUs-associated hypoglycemia in patients with type 2 DM. The mechanism of SUs is mediated by an inhibitory effect on ATP-sensitive potassium channels, SUR, and Kir6.x receptors present both in pancreatic β-cells and myocardium [21]. Although SUs therapy definitely alters ischemic preconditioning, pro- and antiarrhythmogenic properties of SUs are still under discussion [22].

In patients with type 2 DM, prolonged QTc resulted from decreasing activity of D-dependent protein kinase in voltage-dependent potassium channels. The association of hypokalemia and hypoglycemia additionally intensifies repolarization disorder. At the same time, myocardial mitochondrial oxidative stress affects Ca2+/calmodulin-dependent kinase II, the atrial concentration of which is higher in patients with type 2 DM with reported hypoglycemic episodes [23]. ATP-sensitive potassium channels in the sinoatrial area during the administration of their inhibitors are characterized by proarrhythmic effects [24]. A decrease in ischemic preconditioning and proarrhythmic effect associated with ATP-sensitive potassium channel closure depends on the patient's age [25].

Carbohydrate disorder-associated proarrhythmic factors are an altered phosphoinositol mechanism, ion flux dysfunction, disorders related to ATP-sensitive potassium channels, action potential, expression of receptors, and glucose transporters in cardiomyocyte sarcolemma [26]. It was established that an increased concentration of advanced glycation end products worsens ventricular cardiomyocyte fibrosis. Moreover, proinflammatory and profibrotic cytokines myocardial inducing cardiac remodeling are produced by epicardial and pericardial adipose tissues [27].

Multi-center, randomized clinical trials confirmed that cardiovascular complications were associated with high hyperglycemia or highly strict glycemic control [28].

The study was limited by a "SU administration" criterion indicative of the most common hypoglycemic therapy in patients with type 2 DM associated with myocardial dysfunction [29]. Intraclass stratification of glucose and cardiac monitoring parameters for different SUs is of interest. The results of glucose and cardiac monitoring in patients in patients with severe prior cardiovascular diseases excluded from the study are to be evaluated. Glucose and cardiac monitoring in patients admitted to the endocrinology inpatient department was also a limitation. However, baseline parameters of the study sample met mean values mentioned in the Russian National Register of Diabetes Mellitus and were consistent with general population values [30].

Summary

Synchronous glucose and cardiac monitoring in patients with a long history of type 2 DM, receiving SUs, confirmed, and detailed a relationship between the quality of glycemic control and onset of cardiovascular diseases.

Poor quality of glycemic control is associated with the onset of cardiovascular diseases, e.g., hypoglycemia

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is associated with QTc prolongation, ST depression and VAs, and high hyperglycemia with VAs.

Cardiovascular diseases are mainly associated with worse glycemic control: high glycemic variability determines the prolongation of QTc interval, ST depression, and VAs. High hyperglycemia is associated with VAs, and the hypoglycemic region with prolonged QTc, ST depression, and VAs.

Conclusion

Patients with a long history of type 2 DM receiving SUs are the most susceptible to cardiovascular complications. Synchronous glucose and cardiac monitoring enable a precise quantitative evaluation of cardiometabolic status in patients with type 2 DM and personalization of management objectives intended to reduce glycemic variability and eliminate hypo- and hyperglycemic conditions, thus, mitigate cardiovascular consequences in patients with type 2 DM. Glucose and cardiac monitoring should be implemented extensively in real-world clinical practice.

No conflict of interest is reported.

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